REMARKS

Claims 1-21 are pending and stand rejected on a variety of grounds. Claim 1 has been amended to recite "whereby the direct illumination of the fluorophore directly excites the fluorophore..." Support for this clarifying amendment can be found throughout the Claims and the specification, for example, at paragraphs **0045**, **0005**, **0006,** and **0060**. Additionally, support can be found in the Examples (paragraphs **0085-0096**). The amendment adds no new matter.

Applicants were pleased to note that the previous rejections under 35 U.S.C. §112, second paragraph, 35 U.S.C. §102(b) over Hesselberth, 35 U.S.C. §103(a) over Lee in light of Potyrailo and over Potyrailo in light of Fang were withdrawn in the Final Office Action. Each of the current rejections is addressed below.

Rejections under 35 U.S.C. §102 - General Considerations

Several of the Claims stand rejected under 35 U.S.C. §102 as anticipated by one or more references. Section 2143 of the M.P.E.P. states that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Applicants direct the Examiner's attention to the fact that Claim 1 recites identifying the presence or amount of an analyte when the anisotropy measurement is greater than the anisotropy measurement in the absence of the analyte. Disclosure of an increase in anisotropy upon binding has not been addressed in any of the rejections set forth in the current Office Action.

Additionally, as discussed during the interview, one of the differences between the claimed invention and the cited references is the particular combination of surface associated anisotropy measurements and direct illumination. Applicants note that prior to their invention, people had used low noise techniques to measure anisotropy for surface attached probes, as demonstrated in the papers cited by the Examiner. Examples of such techniques are evanescent wave or FRET-based techniques. Generally, these techniques result in low background noise, allowing for small changes in light intensity to be observed. These techniques were thought to be required for surface bound fluorophores because they had less mobility, and thus less ability to

undergo a change in anisotropy upon binding, as discussed below and in previous papers. This belief would have led the skilled artisan away from the presently claimed invention. As a result, Applicants believe that they were the first to discover that a surface associated aptamer and fluorophore, when excited by the previously assumed noisy technique of direct light illumination, would practically produce a large enough change in anisotropy upon binding to allow binding to be detected through a change in anisotropy. Moreover, even if such a possibility were recognized, there is no present teaching of this in the cited art.

Rejection under 35 U.S.C. §102(b) Potyrailo et al.

Claims 1, 8, and 16 stand rejected under 35 U.S.C. §102(b) as being anticipated by Potyrailo et al. (Potyrailo et al., Anal Chem, 70:3419-3425 (1998), herein after "Potyrailo"). It is asserted by the Examiner that Potyrailo teaches an anti-thrombin DNA aptamer immobilized to a glass surface and that fluorescence anisotropy is used to detect analyte binding with the aid of a vertically polarized laser. Applicants respectfully disagree.

As discussed in the phone interview of March 8, 2005, Potyrailo does not teach or suggest measuring the anisotropy of a fluorophore through the direct illumination of the fluorophore. Rather, Potyrailo addresses indirect illumination and excitation of the fluorophore, *e.g.*, through evanescent wave formation. All of the actual teachings in Potyrailo are directed to anisotropy measurements through evanescent field illumination.

The section of Potyrailo cited by the Examiner that mentions direct illumination does so only to emphasize the need for using evanescent wave illumination in the process they are describing. Moreover, the references cited in this section are general references that discuss the advantages and need for evanescent wave illumination. They are not directed towards using direct illumination or for using direct illumination instead of evanescent wave illumination on solid surfaces. As discussed in the interview, the section does not imply or suggest that direct illumination is an alternative technique to evanescent wave illumination. If anything, this section and the references it cites demonstrate that direct illumination and evanescent wave illumination are not interchangeable. The section itself implies that evanescent wave illumination is required in Potyrailo's arrangement, as it has "an important advantage" over direct sample illumination.

As Potyrailo does not teach each of the elements, Applicants request that the rejection be withdrawn and the claims allowed.

Rejection under 35 U.S.C. §102(b) Fang et al.

Claims 1, 17-19, and 21 stand rejected under 35 U.S.C. §102(b) as being anticipated by Fang et al. (hereinafter "Fang"). 35 U.S.C. §102(b) requires that to be available as prior art the reference be published more than one year prior to the filing date of the application. The present claims are entitled to a priority date of August 2, 2002, based on the filing of U.S. provisional Application No. 60/401,021. The earliest possible publication date for Fang is November 03, 2001. Thus, Fang was published less than a year prior to the effective filing date of the present application and is not available as prior art under §102(b).

Additionally, the Applicants note that while Fang states that a general concept taught in Fang could be applied to biosensors, for support for this idea, Fang actually cites Potyrailo, which has the failings discussed above regarding its failings to teach direct illumination, and two other references, neither of which involve anisotropy measurements.

Thus, the Applicants note that in arguing the rejection, the Examiner has had to pick and choose which sections of Fang to include and which teachings of other references to include, as well as how to combine the teachings. As the combination of each of the elements is not taught, the Applicants request that the rejection be withdrawn and the claims allowed.

Rejection under 35 U.S.C. §102(e) Stanton et al.

Claims 1, 2, 7-9, and 11-21 also stand rejected under 35 U.S.C. §102(e) as being anticipated by Stanton et al (U.S. Pat. No.: 6,680,377, hereinafter "Stanton"). The Examiner found that Stanton teaches aptamer beacons comprising aptamers configured to bind to specific target molecules that can be attached to a solid support at different predetermined points in a one or two-dimensional array such as on a particle or plate. Upon binding of the aptamer beacon to a target molecule, concomitant signals such as fluorescence anisotropy can be generated. Applicants respectfully submit that Stanton does not teach the claimed method.

Stanton is directed to anisotropy measurements via an evanescent wave. As a result, it does not teach or suggest directly illuminating the fluorophore as recited in Claim 1 as amended: "whereby the direct illumination of the fluorophore directly excites the fluorophore." As each of the elements of Claim 1 is not taught, Applicants request that the rejection be withdrawn and the claims allowed.

Rejection under 35 U.S.C. §102(b) Lakowicz

Claims 1, 9, 10, and 16 stand rejected under 35 U.S.C. §102(b) as being anticipated by Lakowicz (U.S. Pat. No.: 5,631,169). The Examiner has asserted that Lakowicz teaches a fluorometric luminescence immunoassay comprising the steps of exciting a sample with radiation from any suitable radiation source, such as a laser, where the sample comprises a first reactant bound to polymeric supports and a second reactant supplied in solution or suspension. Applicants respectfully submit that these teachings do not anticipate the presently claimed invention.

Applicants note that Lakowicz is concerned with a FRET based system. As discussed in the interview, the presently amended Claim 1 clarifies the fluorophore is directly illuminated and directly excited by the illumination. In contrast, a FRET based system relies on indirect illumination or indirect excitation of the fluorophore.

Additionally, Applicants note that present Claim 1 recites a fluorophore labeled aptamer. There is no teaching in Lackowicz of an aptamer.

As each of the elements of Claim 1 is not taught by Lackowicz, Applicants request that the rejection be withdrawn and the claims allowed.

Rejection under 35 U.S.C. §102(e) Gold et al. in light of Fang et al

Claims 1, 9, 11, 12, 14, and 17-21 stand rejected under 35 U.S.C. §102(e) as being anticipated by Gold et al. (U.S. Pat. No.: 6,544,776, hereinafter "Gold") in light of Fang et al. (Anal. Chem., 73:5752-5757, (2001), hereinafter "Fang"). It is asserted that Gold teaches aptamers immobilized to the surface of biochips and measurement of fluorescence anisotropy to determine the presence of target molecules. It is also asserted that Fang defines anisotropy as requiring the use of polarized light. The Examiner concluded that one of skill in the art would logically combine these two references, because polarized light is required for measuring anisotropy. Applicants respectfully traverse.

As discussed in the interview, there are a variety of methods and techniques by which one can illuminate and excite a sample for achieving an anisotropy measurement. One may do so by using an evanescent wave, as disclosed in Potyrailo. Alternatively, one can excite various

fluorophores to excite other fluorophores, for example, through FRET based techniques, as discussed in Lakowicz. These techniques can also be combined.

However, prior to the claimed invention direct illumination and anisotropy measurements for aptamer based technologies was restricted to solution based techniques.

In making this §102 based rejection, the Examiner is essentially asserting that all of these different techniques are the same. This is clearly not the case, as one of skill in the art would recognize the differences in the techniques and the advantages and disadvantages of each.

Applicants further submit that one of skill in the art would not use a method for measuring solution-based changes in anisotropy to measure support-based changes in anisotropy, especially when the art does not consider the techniques to be interchangeable. Indeed, as discussed in more detail below, Applicants submit that such a combination is inadequate, even under a 35 U.S.C. §103 analysis.

Additionally, Applicants note that Gold explicitly teaches a method of measuring support-based anisotropy, via an evanescent field, similar to that in Potyrailo (Col. 19, lines 15-47). One of skill in the art would not ignore the explicit teachings of Gold, which are directly applicable to the field's previous understanding of support-based anisotropy measurements in this technology.

As there are clearly different techniques for illumination, and Gold requires a choice as to which technique to use, this reference cannot anticipate the present claims.

In light of the above arguments, Applicants request that the rejection under 35 U.S.C. §102(e) be withdrawn and Claims 1, 9, 11, 12, 14, and 17-21 be allowed.

Rejections under 35 U.S.C. §103(a) Fang et al. in light of Lee

The Examiner has rejected Claims 2-9, 11-13, 17-19, and 21 under 35 U.S.C. §103 as being obvious in view of the combination of Fang and Lee ("A fiber-optic microarray biosensor using aptamers as receptors," 2000, *Anal Biochem.*, 282:142-146, hereinafter "Lee").

Section 2143 of the M.P.E.P. recites the three basic requirements for establishing a *prima facie* case of obviousness. First, the cited reference (or references when combined) must teach or suggest all of the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success.

The Examiner asserts that Fang teaches the detection of oncoprotein PDGF, a potential protein marker for cancer diagnosis, using fluorescence anisotropy where fluorescence measurements were performed on a spectrofluorometer after illumination with polarized light. Further, the Examiner asserts that Fang teaches that the detection of PDGF using fluorescence anisotropy is expected to be sensitive, convenient, selective, quick, and can detect PDGF down to 0.22nM. Further that Fang teaches that this assay component can be used for biosensors by immobilization of the aptamer onto a solid. Furthermore, that Lee teaches silica beads and fluorescent measurements. It is asserted that the motivation for combining these references is that it would provide an assay for an oncoprotein and disease related protein detection that is quick, sensitive, convenient, and selective. The Applicants respectfully traverse.

First, as discussed above, Fang itself does not teach the claimed combination of steps. Rather, the Examiner has had to pick and choose which sections of Fang to combine in order have a teaching that is similar to the claimed invention. For example, Fang does not actually suggest that illumination and excitation of an immobilized fluorophore and subsequent measurement of its anisotropy should be done through direct illumination and direct excitation as opposed to the evanescent wave technique taught in Potyrailo. This deficiency is not made up for by any of the secondary references. As such, not every element of the claimed invention is taught.

Additionally, Applicants note that the motivation asserted by the Examiner is not an adequate motivation to explain why one of skill in the art would have combined these two references, as all of the motivation is achieved within Fang alone. Moreover, the motivation is a general motivation as to why one might combine Fang with any other reference, and does not supply a motivation as to why Fang would be combined with Lee in particular.

Thus, a *prima facie* case of obviousness has not been established. As such, Applicants request that the rejection be withdrawn and Claims 1-9, 11-13, 17-19, and 21 allowed.

Conclusion

Applicants respectfully submit that for the above-recited reasons the rejections should be withdrawn. Applicants respectfully submit that the present application is in condition for

allowance. If, however, some issue remains, the Examiner is cordially invited to telephone the undersigned in order to resolve such issue promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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